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Citation for published version:

Tripathi, D, Therapondos, G, Ferguson, JW, Newby, DE, Webb, DJ & Hayes, PC 2006, 'Endothelin-1 contributes to maintenance of systemic but not portal haemodynamics in patients with early cirrhosis: a randomised controlled trial', *Gut*, vol. 55, no. 9, pp. 1290-5. <https://doi.org/10.1136/gut.2005.077453>

Digital Object Identifier (DOI):

[10.1136/gut.2005.077453](https://doi.org/10.1136/gut.2005.077453)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Gut

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LIVER DISEASE

Endothelin-1 contributes to maintenance of systemic but not portal haemodynamics in patients with early cirrhosis: a randomised controlled trial

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Gut 2006;55:1290-1295. doi: 10.1136/gut.2005.077453

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Revised version received
12 January 2006
Accepted for publication
15 January 2006
Published online first
24 January 2006

Background and aims: Increased endothelin (ET)-1 activity may contribute to the complications of cirrhosis and portal hypertension. The aim of this study was to assess the systemic and portal haemodynamic effects of selective ET-A and ET-B receptor antagonism in patients with cirrhosis.

Methods: Sixteen patients with cirrhosis and portal hypertension (aged 52 (1) years, Pugh score 6.2 (0.3)) underwent 24 studies with infusions of: (A) selective ET-A antagonist, BQ-123 (n=8), at 1000 and 3000 nmol/min; (B) selective ET-B antagonist, BQ-788 (n=8), at 100 and 300 nmol/min; or (C) matched saline placebo (n=8) in a double blind randomised manner. Haemodynamic measurements were performed through pulmonary artery, hepatic venous, and femoral artery catheters.

Results: Baseline patient characteristics were well matched. Compared with placebo, BQ-123 decreased mean arterial pressure (MAP -15 (11) mm Hg (-18%); $p<0.02$) and pulmonary vascular resistance index (PVRI -81 (54) dyn \times s \times m²/cm⁵ (-64%); $p<0.05$), with no effect on hepatic venous pressure gradient (HVPG), cardiac index (CI), or systemic vascular resistance index (SVRI). Compared with placebo, BQ-788 increased MAP (+11 (3) mm Hg (+12%); $p<0.03$) and SVRI (+1101 (709) dyn \times s \times m²/cm⁵ (+50%); $p<0.05$), reduced CI (-1.0 (0.4) l/min/m² (-29%); $p=0.05$) with no effect on HVPG or PVRI.

Conclusions: ET-1 contributes to maintenance of systemic and pulmonary haemodynamics without acutely affecting HVPG in patients with early cirrhosis. In this group of patients, the use of selective ET-A and ET-B antagonists for the management of variceal haemorrhage is likely to be limited.

Endothelin-1 (ET-1) was first identified by Yanagisawa and colleagues in 1988¹ and is one of three 21 amino acid peptides ET-1, ET-2, and ET-3. ET-1 has marked vascular actions and is formed in the endothelium, liver, and other tissues from the 38 amino acid precursor big ET-1 by endothelin converting enzyme.² ET-1 binds to two G coupled receptors: endothelin-A (ET-A) and endothelin-B (ET-B) receptors.³ Both receptors are found in vascular smooth muscle where they mediate vasoconstriction, whereas in the endothelium, ET-B receptors mediate vasodilatation in part through nitric oxide release.³ Through these receptors, ET-1 provides a major contribution to maintenance of basal vascular tone and blood pressure in humans.⁴

Plasma ET-1 concentrations are three times higher in patients with cirrhosis than in healthy controls.⁵ The concomitant rise in plasma big ET-1 concentrations suggests that this is predominantly due to increased ET-1 synthesis. The hepatic stellate cell (HSC) contributes to regulation of intrahepatic resistance and is the primary hepatic origin of increased ET-1 synthesis.⁵ Outside the liver, there are other potential sources, including the kidney and vascular endothelium, that may increase ET-1 release in response to splanchnic arterial vasodilatation.⁶ In addition to increased plasma ET-1 concentrations,^{7,8} patients with cirrhosis have altered ET-A and ET-B receptor gene expression on HSC⁹ which correlates with the degree of portal hypertension in human subjects.¹⁰ It is proposed that elevated concentrations of ET-1 act on upregulated ET receptors on the HSC to cause increased contractility and intrahepatic sinusoidal resistance, resulting in portal hypertension. Furthermore, in the injured liver, there appears to be a concurrent reduction in the

intrahepatic production of vasodilators, such as nitric oxide,¹¹ leading to an imbalance in vascular mediators favouring vasoconstriction that further exacerbates increased contraction of the HSC.

We hypothesised that inhibition of the endothelin system in patients with liver cirrhosis and portal hypertension would reduce portal pressure. Animal studies have supported this hypothesis and demonstrated a fall in portal pressure with both ET-A and ET-B receptor antagonism.¹²⁻¹⁵ Clinical studies on forearm circulation have shown altered activity of the endothelin system in cirrhosis, and that ET-1 contributes to maintenance of basal vascular tone in patients with cirrhosis.^{16,17} To date, there have been no controlled clinical studies to investigate the acute haemodynamic effects of systemic endothelin receptor antagonism in patients with cirrhosis.

The aim of this randomised, double blind, placebo controlled study was to investigate the acute systemic, pulmonary, and portal haemodynamic effects of selective ET-A and ET-B receptor antagonism in patients with cirrhosis and portal hypertension.

Abbreviations: ET-1, endothelin-1; ET-A, endothelin A; ET-B, endothelin B; MAP, mean arterial pressure; PVRI, pulmonary vascular resistance index; HR, heart rate; SVRI, systemic vascular resistance index; HSC, hepatic stellate cell; HVPG, hepatic venous pressure gradient; FHVP, free hepatic venous pressure; WHVP, wedged hepatic venous pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedged pressure; MPAP, mean pulmonary artery pressure; RAP, right atrial pressure; CO, cardiac output; CI, cardiac index; HBF, hepatic blood flow; ICG, indocyanine green; PPHT, portopulmonary hypertension

PATIENTS AND METHODS

Patients

Patients with cirrhosis and portal hypertension were recruited to the study with the approval of the local research ethics committee, written informed consent from each subject, and in accordance with the Declaration of Helsinki of the World Medical Association. All patients with alcoholic liver disease abstained from alcohol for at least one month prior to and during the study period, confirmed by random serum ethanol testing. All studies were performed following an overnight fast. Exclusion criteria were age <18 or >75 years, regular vasoactive medication, hepatic venous pressure gradient (HVPG) <8 mm Hg, portal vein thrombosis, a surgical portosystemic shunt or transjugular intrahepatic portosystemic shunt, significant comorbidity, malignant disease, pregnancy, and women of childbearing potential.

Haemodynamic measurements

All haemodynamic measurements and blood sampling were performed in the supine position after an overnight fast and starting at 08:00. After infiltration with 10 ml of 2% lidocaine, a 9F introducer sheath (Avanti; Cordis Europa, Roden, the Netherlands) was inserted into the right femoral vein using the Seldinger technique. Under fluoroscopic guidance, a Swan Ganz balloon tipped catheter (Edward Lifesciences Corporation, Irvine, California, USA) was inserted into the main right hepatic vein for measurement of the free (FHVP) and wedged (WHVP) hepatic venous pressures, respectively. All measurements were taken on a recorder capable of producing permanent readings and designed for both venous and arterial measurements (Hewlett Packard series 54 model 78339A). FHVP was measured with the catheter advanced into the hepatic vein within 5 cm of the vena cava and after stabilisation for up to 30 seconds. WHVP was obtained with the balloon inflated and after stabilisation of tracings for up to a minute. Measurements were repeated every 10 minutes with the catheter in the same position, and by the same operator. HVPG was defined as the difference between WHVP and FHVP.

Using the same technique, a second 9F introducer sheath (Avanti; Cordis Europa, Roden, the Netherlands) was inserted into the right femoral vein. Through this, a continuous cardiac output catheter (Edward Lifesciences Corporation, Irvine, California, USA) was passed to the pulmonary artery for measurement of free pulmonary artery pressure (PAP), pulmonary artery wedged pressure (PAWP), and mean PAP (MPAP). Right atrial pressure (RAP), cardiac output (CO), and mixed venous oxygen saturation were measured continuously using a Baxters Vigilance monitor (Edward Lifesciences Corporation). Cardiac index (CI) was calculated as CO/body surface area.

The femoral artery was cannulated using an arterial catheter (Leader Cath; Vygon, Aachen, Germany) for continuous measurement of arterial blood pressure (Hewlett Packard series 54 model 78339A) and blood sampling. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus a third of pulse pressure.

Systemic vascular resistance index (SVRI) was calculated as:

$$80 \times (\text{MAP} - \text{RAP})/\text{CI}.$$

Pulmonary vascular resistance index (PVRI) was calculated as:

$$80 \times (\text{MPAP} - \text{PAWP})/\text{CI}.$$

Blood assays

Blood samples were obtained from the femoral vein in the supine position after 30 minutes of rest. Blood (10 ml) was admixed with 1 ml of 1% disodium EDTA and 1000 KIU

aprotinin (Bayer AG, Leverkusen, Germany). Samples were immediately placed on ice and centrifuged at 1500 *g* for 20 minutes. Plasma was frozen and stored at -80°C until assayed. Following extraction using Bond Elut columns (Varian, Harbor City, California, USA), plasma concentrations of ET-1 (Peninsula Laboratories Europe Ltd, St. Helens, UK) and big ET-1 (Peninsula Laboratories Europe Ltd) were determined by radioimmunoassay, as described previously.¹⁸ Intra-assay coefficients of variation for ET-1 and big ET-1 were 7.0% and 7.2%, respectively, and interassay coefficients of variation were 9.0% and 9.3%, respectively.

Measurement of hepatic blood flow

Hepatic blood flow (HBF) was derived from measurement of indocyanine green (ICG; Pulsion Medical Systems AG, Munchen, Germany) clearance and extraction.¹⁹ ICG was infused at the beginning of the study as a 10 mg intravenous bolus followed by an infusion of 0.2 mg/min ICG. After an equilibration period of 50 minutes, samples were taken simultaneously from the right hepatic vein and peripheral femoral vein in triplicate. Further samples were taken at 80 and 130 minutes. Peripheral and hepatic samples were centrifuged at 1500 *g* for 20 minutes, and the optical density of the supernatant determined. The value for optical density was then plotted on a standard graph and the per cent concentration extrapolated. The following formula was next used to calculate HBF:

$$\text{HBF} = (\text{ICG clearance}/\text{ICG extraction})/(1 - \text{haematocrit}) \\ = (Q/(\text{Cp} - \text{Ch}))/(1 - \text{Haematocrit})$$

where Q is the infusion rate of ICG at 0.2 mg/min, and Cp and Ch are peripheral and hepatic per cent concentrations of ICG, respectively, derived as above. The final value for HBF has to be multiplied by a factor of 100 to derive HBF in ml/min. This method cannot be used if hepatic excretion (Cp - Ch) is less than 10%.

Study protocol

This was a randomised, double blind, placebo controlled trial. At the start of each study, 30 minutes was allowed for equilibration of haemodynamic measurements. Patients were then randomised to receive one of the following agents at times 0 and 80 minutes: (1) pharmaceutical grade BQ-123 (Clinalfa AG, Läufelfingen, Switzerland) dissolved in saline given at 1 ml/min at a dose of 1000 nmol/min, followed by a further dose of 3000 nmol/min for 20 minutes at each dose^{20 21} (protocol A, ET-A receptor antagonism); (2) pharmaceutical grade BQ-788 (Clinalfa AG, Läufelfingen, Switzerland) dissolved in saline given at 1 ml/min at a dose of 100 nmol/min and 300 nmol/min for 20 minutes at each dose^{20 21} (protocol B, ET-B receptor antagonism); or (3) matched saline placebo administered twice (protocol C). Patients were invited to attend for up to three independent studies, with one study performed per day, and a separate randomisation schedule was used for each patient to prevent repetition of studies.

Statistical analysis

All results are expressed as mean (SD). All baseline haemodynamic parameters were calculated after the 30 minute period allowed for equilibrium. Parametric data were analysed using the Student's *t* test and Pearson's correlation as summary measures.²² The peak difference for each haemodynamic variable was compared using the Student's *t* test. The Wilcoxon signed rank test and Spearman regression analysis were used for non-parametric data. Statistical analysis was performed using SPSS (version 9, Chicago, Illinois, USA), and significance was taken at the 5% level. Based on previous studies, we had a 90% power of detecting a placebo adjusted clinically significant difference in: CI of

Table 1 Baseline clinical data

Variable	Placebo (n = 8)	BQ-123 (n = 8)	BQ-788 (n = 8)
Age (y) (mean (SD))	50 (4)	54 (7)	52 (9)
Sex (M/F)	8/0	7/1	8/0
Body mass index (kg/m ²)	23 (3)	24 (2)	25 (3)
Child-Pugh score	6 (2)	6 (2)	6 (1)
Child-Pugh grade (A/B)	5/3	4/4	5/3
Ascites present	2	2	1
Varices	8	7	8
Bilirubin (μmol/l)	29 (16)	30 (17)	27 (24)
Albumin (g/l)	38 (6)	38 (8)	41 (7)
Prothrombin time (s)	12 (2)	11 (3)	11 (2)
Big ET-1 (pg/ml)*	79 (30)	68 (24)	60 (15) (n = 7)
ET-1 (pg/ml)†	8 (3)	7 (2)	7 (1) (n = 7)
Aetiology			
Alcoholic	6	5	6
Hepatitis C	2	3	2

Values are expressed as mean (SD).

ET, endothelin.

*Normal range 20–60 pg/ml.

†Normal range 0.5–5 pg/ml.

0.37 l/min/m², total peripheral vascular difference of 3.3 Wood units, MAP of 5.5 mm Hg, heart rate (HR) of 5.5 bpm, HBF of 32.5 ml/min, and HVPG of 3.1 mm Hg.

RESULTS

Of the 22 eligible patients, 18 patients were recruited into the study. Four studies were terminated before completion due to technical failure of instrumentation (n = 2), new onset of atrial fibrillation (n = 1), or low HVPG of 4 mm Hg (n = 1). One patient completed three studies, six completed two studies each, and nine completed one study only, resulting in 24 studies in 16 patients. In patients who completed more than one study, the mean time interval between studies was 61 (10) days. Baseline clinical characteristics of the patients were well matched although WHVP was lower for patients administered BQ-788 compared with placebo (tables 1, 2).

Systemic haemodynamic effects

Compared with placebo, BQ-123 reduced MAP (peak change −15 (11) mm Hg (−18%); p < 0.05) (fig 1) with a reflex increase in HR (peak change +19 (7) bpm (+25%); p < 0.05)

and reduction in RAP (peak change −4 (3) mm Hg (−82%); p = 0.003) but no effect on CI. There was a trend towards a reduction in SVRI with BQ-123 (peak change −1194 (866) dyn × s × m²/cm⁵ (−62%); p = 0.051). BQ-788 increased MAP (peak change +11 (3) mm Hg (+12%); p < 0.05) (fig 1) and SVRI (peak change +1101 (709) dyn × s × m²/cm⁵ (+50%); p < 0.05), accompanied by a reduction in CI (peak change −1 (0.4) l/min/m² (−29%); p = 0.05) with no effect on HR or RAP.

Portal haemodynamic effects

HVPG did not change following administration of either drug compared with placebo or when comparing the two drugs (fig 2). It was not possible to derive HBF in seven studies due to the hepatic excretion of ICG being less than 10%. The data available did not reveal any changes in HBF following administration of either BQ-788 (n = 7) or BQ-123 (n = 6) compared with placebo (n = 4).

Pulmonary haemodynamic effects

Compared with placebo, BQ-123 appeared to reduce MPAP (peak change −4 (3) mm Hg (−29%); p = 0.08) and reduced

Table 2 Baseline haemodynamic variables

Variable	Placebo (n = 8)	BQ-123 (n = 8)	BQ-788 (n = 8)
Systemic haemodynamics			
HR (beats/min)	85 (20)	76 (9)	77 (17)
MAP (mmHg)	87 (17)	86 (11)	87 (10)
CI (l/min/m ²)	4 (1)	5 (3)	4 (2)
SVRI (dyn × s × m ² /cm ⁵)	1960 (1046)	1935 (1141)	2148 (949)
Portal haemodynamics			
WHVP (mm Hg)	24 (4)	22 (6)	18 (4)*
FHVP (mm Hg)	5 (4)	6 (2)	5 (4)
HVPG (mm Hg)	19 (5)	16 (6)	13 (4)
HBF (ml/min)†	853 (397) (n = 4)	922 (925) (n = 6)	701 (283) (n = 7)
ICG hepatic concentration (mg/ml)	2 (1.5)	8 (17)	5 (10)
ICG peripheral concentration (mg/ml)	4 (1.4)	10 (16)	5 (3)
Pulmonary haemodynamics			
PAWP (mm Hg)	4 (2)	5 (5)	5 (3)
RAP (mm Hg)	3 (2)	5 (3)	3 (4)
MPAP (mm Hg)	9 (2)	10 (5)	10 (4)
PVRI (dyn × s × m ² /cm ⁵)	134 (87)	135 (98)	150 (104)

Values are expressed as mean (SD).

HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; SVRI, systemic vascular resistance index; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow; ICG, indocyanine green; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; MPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index.

*p < 0.05 compared with placebo.

†Normal range 400–600 ml/min.²³

n = 8 unless otherwise stated.

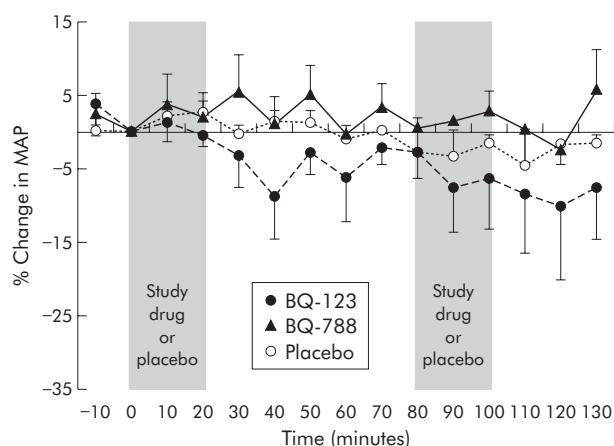


Figure 1 Effects of BQ-123, a selective endothelin (ET)-A receptor antagonist (1000 nmol/min for 20 minutes followed by 3000 nmol/min for 20 minutes) and BQ-788, a selective ET-B receptor antagonist (100 nmol/min for 20 minutes followed by 300 nmol/min for 20 minutes) on mean arterial pressure (MAP) compared with placebo.

PVRI (peak change -81 (54) $\text{dyn} \times \text{s} \times \text{m}^2/\text{cm}^5$ (-64%); $p < 0.05$) (fig 3). BQ-788 had no effect on MPAP or PVRI compared with placebo.

Neurohormonal effects

Compared with placebo, BQ-788 caused an increase in plasma ET-1 concentrations at the higher dose (peak change $+11$ (2) ng/ml ($+69\%$); $p = 0.03$). Compared with placebo, there was no significant change in plasma concentrations of ET-1 following BQ-123 administration, or big ET following administration of either BQ-123 or BQ-788.

Drug tolerability and adverse reactions

In addition to the patients above who were excluded after randomisation, two patients who completed the studies had adverse events. One patient randomised to BQ-788 developed a vasovagal response to catheter withdrawal and responded promptly to intravenous atropine and fluids. Following high dose BQ-123 administration, a second pre-ascitic cirrhotic patient with Child Pugh B disease developed symptomatic hypotension, with MAP falling from 91 to 70 mm Hg. The patient responded promptly to intravenous fluid administration. All patients were followed up in the clinic with no long term side effects.

DISCUSSION

This is the first clinical study to investigate the acute haemodynamic effects of selective ET-A and ET-B receptor antagonism in patients with cirrhosis and portal hypertension. Using a rigorous randomised, double blind, placebo controlled design, we have demonstrated that selective ET-A and ET-B receptor antagonism reduced and increased systemic blood pressure, respectively, but appeared to have no effect on portal pressure.

In comparison with healthy volunteers where the mean values of baseline plasma ET-1 are between 4 and 5 pg/ml ,²¹ our study population had elevated plasma ET-1 concentrations similar to levels found in patients with early cirrhosis,²⁴ and is consistent with activation of the endothelin system as a result of cirrhosis. Additional elevation of plasma ET-1, but not big ET-1, concentrations with BQ-788 administration supports the continuing role of the ET-B receptor in the clearance of ET-1 in patients with cirrhosis.²¹ We have also demonstrated that both ET-A and ET-B receptors have a role in the maintenance of blood pressure in patients with

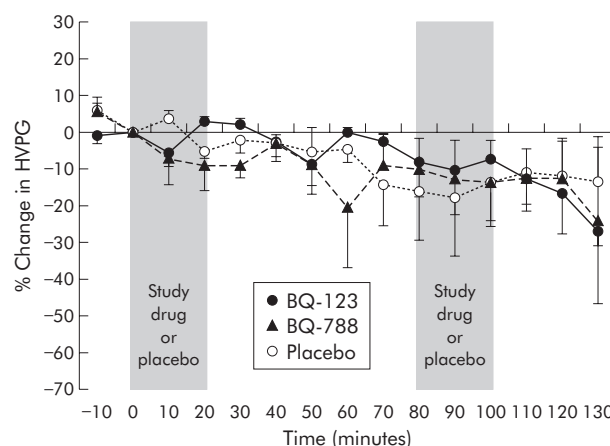


Figure 2 Effects of BQ-123, a selective endothelin (ET)-A receptor antagonist (1000 nmol/min for 20 minutes followed by 3000 nmol/min for 20 minutes) and BQ-788, a selective ET-B receptor antagonist (100 nmol/min for 20 minutes followed by 300 nmol/min for 20 minutes) on hepatic venous pressure gradient (HVPG) compared with placebo.

cirrhosis. The fall in blood pressure seen with BQ-123, and the significant hypotension seen in one subject, suggests increased sensitivity to ET-A receptor antagonism in patients with cirrhosis and is consistent with our previous studies in the peripheral circulation.²⁴ This hypotension was accompanied by a significant reduction in RAP that may reflect reduced pulmonary vascular resistance. A reduction in SVRI with BQ-123, as may be expected, just failed to reach statistical significance ($p = 0.051$), possibly as a result of the wide standard deviation. BQ-788 had the opposite effect on the systemic circulation with an elevation in MAP and SVRI, suggesting that BQ-788 acts mainly by vasoconstriction.

The absence of an effect of intravenous endothelin receptor antagonism on HVPG in patients with cirrhosis and portal hypertension is perhaps surprising. We speculate that this may be explained by the potential contrasting consequences of endothelin antagonism on the dynamic interplay between the collateral, splanchnic, and intrahepatic circulations. One might expect a reduction in intrahepatic resistance by ET blockade and thereby reduce the "backward" component of portal hypertension. In addition, ET-A receptor antagonism

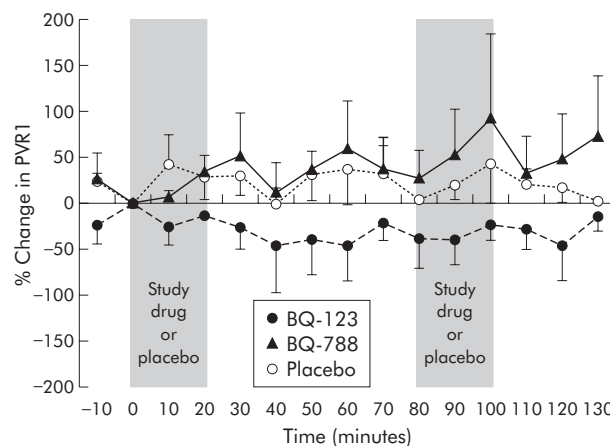


Figure 3 Effects of BQ-123, a selective endothelin (ET)-A receptor antagonist (1000 nmol/min for 20 minutes followed by 3000 nmol/min for 20 minutes) and BQ-788, a selective ET-B receptor antagonist (100 nmol/min for 20 minutes followed by 300 nmol/min for 20 minutes) on pulmonary vascular resistance index (PVRI) compared with placebo.

may result in vasodilatation of the collateral circulation and hence reduce portocollateral resistance.²⁵ However, ET-A receptor antagonism may also cause splanchnic vasodilatation and increase the "forward" component of portal hypertension. Indeed, intravenous ET-1 infusion in healthy volunteers caused abdominal pain and vasoconstriction of the splanchnic circulation,²⁶ suggesting a key role of ET-1 in regulating splanchnic blood flow. Therefore, the theoretical benefits of ET-A receptor blockade with reduced intrahepatic resistance and portocollateral resistance have to be balanced against the potential for splanchnic vasodilatation and maintenance of portal hypertension. A complementary argument could also be made for the absence of an effect with ET-B receptor antagonism, although this is further complicated by ET-B receptor mediated release of vasodilators, such as nitric oxide and clearance of ET-1.²¹

The significant reduction in PVRI with ET-A receptor blockade is an interesting observation of our study. This was accompanied by a strong trend towards reduced MPAP compared with placebo. There has been a lot of recent interest in the use of endothelin receptor antagonists in patients with pulmonary hypertension. Bosentan, a dual endothelin receptor antagonist with 70-fold selectivity for the ET-A receptor, improves symptoms and pulmonary haemodynamics in patients with pulmonary hypertension.^{27–29} This raises the question of whether endothelin antagonism may be beneficial in patients with portopulmonary hypertension (PPHT), although we did not include such patients in our study. Plasma ET-1 concentrations are particularly elevated in those patients with PPHT, implicating a role for ET-1 in the pathogenesis of this condition.³⁰ The effective reversal of pulmonary hypertension would also have major implications for those patients declined hepatic transplantation because of the presence of severe PPHT. However, the use of endothelin antagonists in patients with liver disease does present problems. Both sitaxsentan, an ET-A receptor antagonist, and bosentan have been associated with major disturbances in hepatic function and, in one case with sitaxsentan, led to fatal acute hepatitis.³¹ The adverse effects of bosentan appear to be mediated through impairment in excretion of bile salts and direct hepatotoxicity.³² Whether endothelin antagonism will also produce beneficial haemodynamic effects and improve symptoms in patients with PPHT without causing detrimental effects on the liver requires further careful study.

Study limitations

A potential limitation of the study is that inadequate dosing of antagonists may account for the absence of an effect on portal haemodynamics. We have previously used similar doses to achieve systemic haemodynamic effects in healthy volunteers,^{20–21} and patients with renal³³ and heart failure.³⁴ Two different doses of BQ-123 and BQ-788 were used in the same patient to assess the dose effect, and a lower dose was administered first to ensure that it was tolerated prior to high dose administration. Previous studies on healthy volunteers have also shown that the maximum systemic haemodynamic effects of BQ-123 and BQ-788 occurred at 50–60 minutes, hence a minimum observation period of 50 minutes following administration of these agents.^{20–21} Although we observed changes in systemic haemodynamic variables and plasma ET-1 concentrations, we cannot completely exclude the possibility that the doses used may not have been sufficient to result in effective receptor blockade in the portal circulation. However, the use of higher doses of antagonists is likely to reduce the clinical usefulness of these agents due to the potential for detrimental effects on MAP.

Another limitation of the study is inclusion of three patients with ascites. Ascitic patients are likely to have more unstable haemodynamics, and are at greater risk of

detrimental systemic haemodynamic effects of vasoactive agents.³⁵ However, there were no qualitative differences in the responses to the study drugs between those with and without ascites. Despite inclusion of ascitic patients, most were in Child Pugh class A, and results in patients with more advanced cirrhosis may be different.

It would also be interesting to examine the effect of combined ET-A and ET-B receptor blockade. Studies on cirrhotic rats using the mixed antagonist bosentan have demonstrated significant reductions in portal pressure and hepatocollateral vascular resistance, with minimal systemic effects.¹⁵ In the presence of ET-A receptor antagonism, additional ET-B blockade may cause splanchnic vasodilatation resulting in better tolerance.³⁶ The balance of these effects is unknown but depending on tissue specific receptor expression, this combined approach may or may not provide additional benefits.

In conclusion, this randomised double blind study demonstrates that ET-1 contributes to systemic and pulmonary haemodynamics in patients with early cirrhosis. The lack of an acute effect on portal pressure despite systemic haemodynamic effects suggests that selective endothelin receptor antagonists are likely to have a limited role in the management of variceal bleeding.

ACKNOWLEDGEMENTS

We wish to thank Sharon Cameron and the nursing staff at the Wellcome Trust Clinical Research Facility for all their help with the study. We also acknowledge the assistance of Ms Sue Lieper and Mr Neil Johnston in sample analysis.

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Conflict of interest: None declared.

REFERENCES

- 1 Yanagisawa M, Kurihara H, Kimura S, *et al*. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;**332**:411–15.
- 2 Masaki T, Yanagisawa M, Goto K. Physiology and pharmacology of endothelins. *Med Res Rev* 1992;**12**:391–421.
- 3 La M, Reid JJ. Endothelin-1 and the regulation of vascular tone. *Clin Exp Pharmacol Physiol* 1995;**22**:315–23.
- 4 Haynes WG, Ferro CJ, O'Kane KP, *et al*. Systemic endothelin receptor blockade decreases peripheral vascular resistance and blood pressure in humans. *Circulation* 1996;**93**:1860–70.
- 5 Moore K, Wendon J, Frazer M, *et al*. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. *N Engl J Med* 1992;**327**:1774–8.
- 6 Kapoor D, Redhead DN, Hayes PC, *et al*. Systemic and regional changes in plasma endothelin following transient increase in portal pressure. *Liver Transpl* 2003;**9**:32–9.
- 7 Hartleb M, Kirstetter P, Moreau R, *et al*. Relationships between plasma endothelin concentrations and the severity of cirrhosis. *Gastroenterol Clin Biol* 1994;**18**:407–12.
- 8 Mollier S, Gulberg V, Henriksen JH, *et al*. Endothelin-1 and endothelin-3 in cirrhosis—relations to systemic and splanchnic hemodynamics. *J Hepatol* 1995;**23**:135–44.
- 9 Yokomori H, Oda M, Yasogawa Y, *et al*. Enhanced expression of endothelin B receptor at protein and gene levels in human cirrhotic liver. *Am J Pathol* 2001;**159**:1353–62.
- 10 Leivas A, Jimenez W, Bruix J, *et al*. Gene expression of endothelin-1 and ETA and ETB receptors in human cirrhosis: Relationship with hepatic hemodynamics. *J Vasc Res* 1998;**35**:186–93.
- 11 Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. *Gastroenterology* 1998;**114**:344–51.
- 12 De Gottardi A, Shaw S, Sagesser H, *et al*. Type A, but not type B, endothelin receptor antagonists significantly decrease portal pressure in portal hypertensive rats. *J Hepatol* 2000;**33**:733–7.
- 13 Reichen J, Gerbes AL, Steiner MJ, *et al*. The effect of endothelin and its antagonist Bosentan on hemodynamics and microvascular exchange in cirrhotic rat liver. *J Hepatol* 1998;**28**:1020–30.

- 14 Kojima H, Sakurai S, Kuriyama S, *et al.* Endothelin-1 plays a major role in portal hypertension of biliary cirrhotic rats through endothelin receptor subtype B together with subtype A in vivo. *J Hepatol* 2001;**34**:805–11.
- 15 Sogni P, Moreau R, Gomola A, *et al.* Beneficial hemodynamic effects of bosentan, a mixed ET(A) and ET(B) receptor antagonist, in portal hypertensive rats. *Hepatology* 1998;**28**:655–9.
- 16 Haynes WG, Webb DJ. Contribution of endogenous generation of endothelin-1 to basal vascular tone. *Lancet* 1994;**344**:852–4.
- 17 Helmy A, Newby DE, Jalan R, *et al.* Enhanced vasodilatation to endothelin antagonism in patients with compensated cirrhosis and the role of nitric oxide. *Gut* 2003;**52**:410–15.
- 18 Rolinski B, Sadri I, Bogner J, *et al.* Determination of endothelin-1 immunoreactivity in plasma, cerebrospinal fluid and urine. *Res Exp Med (Berl)* 1994;**194**:9–24.
- 19 Caesar J, Shaldon S, Chianusi L, *et al.* The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin Sci* 1961;**21**:43–57.
- 20 Spratt JC, Goddard J, Patel N, *et al.* Systemic ETA receptor antagonism with BQ-123 blocks ET-1 induced forearm vasoconstriction and decreases peripheral vascular resistance in healthy men. *Br J Pharmacol* 2001;**134**:648–54.
- 21 Strachan FE, Spratt JC, Wilkinson IB, *et al.* Systemic blockade of the endothelin-B receptor increases peripheral vascular resistance in healthy men. *Hypertension* 1999;**33**:581–5.
- 22 Matthews JN, Altman DG, Campbell MJ, *et al.* Analysis of serial measurements in medical research. *BMJ* 1990;**300**:230–5.
- 23 Leevy CM, Mendenhall CL, Lesko W, *et al.* Estimation of hepatic blood flow with indocyanine green. *J Clin Invest* 1962;**41**:1169–79.
- 24 Helmy A, Jalan R, Newby DE, *et al.* Altered peripheral vascular responses to exogenous and endogenous endothelin-1 in patients with well-compensated cirrhosis. *Hepatology* 2001;**33**:826–31.
- 25 Chan CC, Wang SS, Lee FY, *et al.* Endothelin-1 induces vasoconstriction on portal-systemic collaterals of portal hypertensive rats. *Hepatology* 2001;**33**:816–20.
- 26 Bohm F, Pernow J, Lindstrom J, *et al.* ETA receptors mediate vasoconstriction, whereas ETB receptors clear endothelin-1 in the splanchnic and renal circulation of healthy men. *Clin Sci* 2003;**104**:143–51.
- 27 Channick RN, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;**358**:1119–23.
- 28 Sitbon O, Badesch DB, Channick RN, *et al.* Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003;**124**:247–54.
- 29 Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.
- 30 Benjaminov FS, Prentice M, Sniderman KW, *et al.* Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. *Gut* 2003;**52**:1355–62.
- 31 Barst RJ, Rich S, Widlitz A, *et al.* Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. *Chest* 2002;**121**:1860–8.
- 32 Fattinger K, Funk C, Pantze M, *et al.* The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther* 2001;**69**:223–31.
- 33 Goddard J, Johnston NR, Hand MF, *et al.* Endothelin-A receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. *Circulation* 2004;**109**:1186–93.
- 34 Leslie SJ, Spratt JC, McKee SP, *et al.* Direct comparison of selective endothelin A and non-selective endothelin A/B receptor blockade in chronic heart failure. *Heart* 2005;**91**:914–19.
- 35 Forrest EH, Bouchier IA, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. *J Hepatol* 1996;**25**:909–15.
- 36 Verhaar MC, Strachan FE, Newby DE, *et al.* Endothelin-A receptor antagonist-mediated vasodilatation is attenuated by inhibition of nitric oxide synthesis and by endothelin-B receptor blockade. *Circulation* 1998;**97**:752–6.

EDITOR'S QUIZ: GI SNAPSHOT

Tracheal-oesophageal fistula in a patient with lung cancer

Robin Spiller, Editor

Clinical presentation

A 37 year old woman presented with a two month history of a cough. A computed tomography (CT) scan performed in a local hospital demonstrated a mass of the left hilum of the lung and bronchoscopic biopsy confirmed the diagnosis of lung cancer. The patient underwent infusion of antitumour drugs into the bronchial artery and embolisation.

Three weeks postoperatively, the patient developed a cough with sputum, fever, and evidence of aspiration. Five days prior to transfer to our hospital, she deteriorated in spite of antibiotics and full supportive treatment. On arrival, her CT scan demonstrated consolidation in both lower lungs. Subsequently, a non-ionic water soluble contrast swallow examination confirmed a fistula (fig 1). It was evident that the fistula was responsible for the patient's serious symptoms and lung infection.

Question

What was the likely cause of the fistula?

See page 1305 for answer

This case is submitted by:

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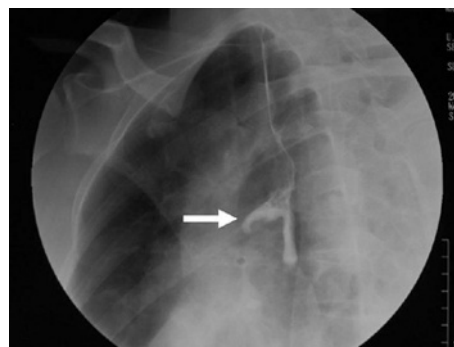


Figure 1 Non-ionic water soluble contrast swallow of the oesophagus (left anterior oblique position). At the T₅ level, the contrast agent extravasated forward into the tracheal cavity (arrow).

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doi: 10.1136/gut.2005.084087